Exhibit C

Expert Opinion

Custirsen (OGX-011): a second-generation antisense inhibitor of clusterin for the treatment of cancer

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Background: Clusterin is a stress-induced cytoprotective chaperone protein, regulated by HSF1, and functions similarly to a small heat-shock protein. Clusterin is expressed in a variety of cancers and associated with broad-spectrum treatment resistance. Custirsen (OGX-011) is a 2′-methoxyethyl modified phosphorothioate antisense oligonucleotide that is complementary to clusterin mRNA; it is currently in clinical trials for patients with cancer. *Objective/methods*: To review the literature on the role of clusterin in cancer progression and treatment resistance, and to summarize completed and ongoing clinical trials with custirsen. *Results/conclusions*: Custirsen is well tolerated in humans and biologically active in inhibiting expression of clusterin in patients with cancer. Randomized trials of custirsen in combination with chemotherapy are planned in patients with castration-resistant prostate cancer.

Keywords: antisense oligonucleotide, cancer, clusterin, custirsen, prostate cancer

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1. Introduction

Development of treatment resistance is a common feature of solid tumor malignancies. A number of mechanisms have been identified that contribute to therapeutic resistance and cancer progression, including increased expression of pro-survival or antiapoptotic genes [1] such as those transcriptionally activated by heat shock factor 1 (HSF1) [2]. HSF1 is the key regulator of the heat shock response, a highly conserved protective mechanism for eukaryotic cells under stress, and has been associated with oncogenic transformation, proliferation and survival [2]. Thus, targeting key gene products regulated by HSF1 and associated with cancer progression and treatment resistance is an attractive and rational therapeutic strategy. Clusterin (also known as testosterone-repressed prostate message 2, apolipoprotein J or sulfated glycoprotein-2) is one such target. This review will summarize its role in cancer and describe the preclinical pharmacology and early clinical trial results for custirsen (OGX-011), a second-generation antisense inhibitor targeting clusterin.

2. The target: clusterin

Human clusterin gene is located in chromosome 8p21-p12, where it is organized into nine exons [3] and encodes for two transcriptional isoforms in humans (Isoform 1, NM_001831 [GenBank]; Isoform 2, NM_203339 [GenBank]). These isoforms result from different transcriptional initiation sites and are produced only in humans and primates. Clusterin isoform 2 is the predominant isoform and encodes for an mRNA of 2kb, which translates to a 449 amino acid protein

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that is highly conserved across species; in humans, clusterin exists as both an intracellular truncated 55 kDa nuclear form and a 75 – 80 kDa secreted heterodimer disulfide-linked glycoprotein [4,5], making clusterin the only known secreted chaperone [6]. The predominant clusterin isoform is a glycoprotein of 75 – 80 kDa containing 22–mer signal peptide chain. The signal peptide targets clusterin to the endoplasmic reticulum (ER) where the 22-mer secretory peptide is removed by proteolytic processing resulting in a 50 kDa clusterin unglycosylated precursor, which is then processed in the ER to a high mannose form of 60 kDa [6]. The 60 kDa precursor translocates to the Golgi, where is cleaved at Arg^{227}-Ser^{228} residues to yield two 40 kDa subunits α- and β-chains. The two subunits are assembled into an antiparallel heterodimeric molecule in which the cysteine-rich centers are linked by five disulfide bridges and are flanked by two coiled coil α -helices and three predicted amphipathic α-helices. The α-helical coiled-coil domains in its α- and β-chains can interact with each other for heterodimerization. The coiled-coil domain is a highly versatile protein folding and oligomerization motif, facilitating its interaction with client proteins involved in many protein signal-transducing events linking clusterin to numerous physiologic and pathologic processes [7]. Clusterin has been described as being both pro-apoptotic [3] and antiapoptotic [8-10]. The secreted form of clusterin has been shown to be cytoprotective and antiapoptotic, whereas the nuclear form is pro-apoptotic [11,12].

Clusterin is overexpressed in a variety of human cancers, including those of the breast, lung, bladder, kidney, colon/rectum and prostate [13-18]. In cancer, clusterin has been largely defined as functioning to inhibit apoptosis. Clusterin is a stress-activated ATP-independent, cytoprotective chaperone [19-22], transcriptionally activated by HSF1, and a potent inhibitor of protein aggregation [23,24]. Clusterin's ability to inhibit apoptosis (see **Figure 1**) has also been shown to act through inhibition of activated Bax, a pro-apoptotic Bcl-2 family member, by sequestering Bax in the cytoplasm and inhibiting cytochrome *c* release [25]. Furthermore, overexpression of clusterin leads to activation of the PI-3Kinase/Akt pathway through the megalin cell surface receptor [8]. In xenograft cancer models, clusterin expression increases in response to cell stress induced by a variety of factors, including standard treatment for cancer [21,22,26,27]. Forced overexpression of clusterin in cancer models confers resistance to radiation, hormone, and chemotherapy, whereas inhibition of clusterin expression enhances apoptotic death from these treatment modalities [19,21,22].

3. Custirsen (OGX-011)

3.1 Chemistry

Antisense oligonucleotide (ASO) therapy is one strategy to specifically target functionally relevant genes. ASOs are chemically modified stretches of single-strand DNA complementary to mRNA regions of a target gene that inhibit translation by forming RNA/DNA duplexes, thereby reducing mRNA and protein levels of the target gene [28]. The specificity and efficacy of an ASO relies on the precise targeting afforded by strand hybridization, where only a perfect match between the target mRNA sequence and the ASO will lead to hybridization and inhibition of translation. The formation of an mRNA-ASO duplex through Watson-Crick binding leads to RNase H-mediated cleavage of the target mRNA. Other proposed mechanisms of antisense action include prevention of mRNA transport, modulation or inhibition of splicing, translational arrest, and formation of a triple helix via ASO binding to duplex genomic DNA resulting in inhibition of transcription. Additionally, 'off-target' effects include immunostimulatory activity, especially in ASO containing CpG motifs or strings of G, or apatomer-like ASO-protein interactions. Phosphorothioate ASOs are water-soluble, stable agents resistant to nuclease digestion through substitution of a non-bridging phosphoryl oxygen of DNA with sulfur [29]. In clinical trials, a major technical limitation with the first generation of phosphorothioate ASOs was the requirement for continuous or frequent intravenous infusions because of the short tissue half-life of these agents. Therefore, effort has been made to improve the stability and efficacy of ASO by modifications of the phophodiester linkage, the heterocycle or the sugar. One such alteration is the 2′-*O*-(2-methoxy) ethyl (2′-MOE) modification to the 2′-position of the carbohydrate moiety. 2′MOE ASOs form duplexes with RNA with a significantly higher affinity relative to unmodified phosphorothioate ASOs. This increased affinity has been shown to result in improved antisense potency *in vitro* and *in vivo*. In addition, 2′MOE ASOs display significantly improved resistance against nuclease-mediated metabolism relative to first-generation phosphorothioate ASOs, resulting in an improved tissue half-life *in vivo*, which produces a longer duration of action and allows for a more relaxed dosing regimen [30]. Finally, these second-generation phosphorothioate ASOs have the potential for a more attractive safety profile relative to unmodified phosphorothioate ASOs [31].

Custirsen is a 21-nucleoside ASO complementary to the clusterin exon II mRNA AUG translation initiation site, with one CpG motif. The custirsen sequence was identified as the most potent to inhibit clusterin expression after the gene was 'walked' with a series of antisense sequences. Custirsen is a second-generation phosphorothioate and incorporates the 2′MOE modification with four 2′MOE-modified nucleosides at the 3′ side, four 2′MOE-modified nucleosides at the 5′ side and thirteen 2′-deoxyribonucleosides in between (referred to as a 4-13-4 MOE gapmer).

3.2 Pharmacodynamics

Custirsen is a potent inhibitor of clusterin expression in *in vitro* and *in vivo* laboratory models [30]. Furthermore, there is specificity for custirsen to inhibit only the expression of the antiapoptotic secreted form of clusterin, with no

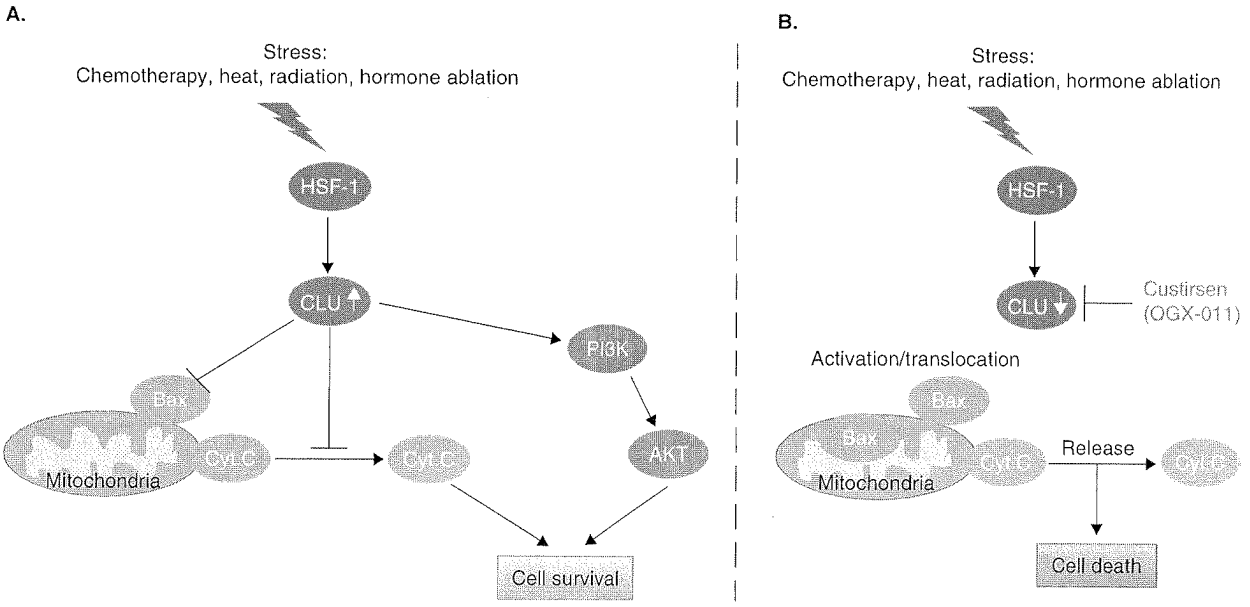

Figure 1. Clusterin is a stress-activated, multifunctional cytoprotective chaperone. A. Under stress conditions (chemotherapy, heat, radiation, hormone ablation), clusterin is overexpressed via activation of HSF-1. Clusterin overexpression interferes with Bax activation and sequesters Bax in the cytoplasm, thereby blocking cytochrome C release and inhibiting cell apoptosis. Clusterin overexpression also enhances activation of PI3K/AKT, a major survival pathway in cancer cells. **B.** Knockdown of clusterin using Custirsen (OGX-011) targets the intrinsic apoptotic pathway by facilitating activation of Bax and its translocation to the mitochondria, leading to cytochrome c release and cell apoptosis.

effect on the pro-apoptotic nuclear form [32]. Unmodified phosphorothioate ASOs have relatively short serum and tissue half-lives (< 2 and 4 h, respectively) and only small amounts of full-length ASO can be detected in tissues after 24 h. By contrast, intermittent dosing of custirsen was as biologically effective as continuous dosing of a unmodified phosphorothioate with the same sequence [30]. In preclinical efficacy studies, custirsen has been shown to significantly enhance the therapeutic effect of hormone therapy, chemotherapy, and radiation therapy in a variety of tumor models, including prostate, breast, non-small cell lung, bladder, and kidney [33].

The first-in-man Phase I study with custirsen used a novel neoadjuvant design to identify effective biologic dosing of custirsen to inhibit clusterin expression in human cancer. Twenty-five male patients with localized prostate carcinoma and high-risk features were treated with custirsen given as a 2-h intravenous infusion prior to radical prostatectomy within 7 days of the last OGX-011 dose. This was a dose-escalation study in which doses of 40 mg (1 patient), 80 mg (3 patients), 160 mg (3 patients), 320 mg (6 patients), 480 mg (6 patients) or 640 mg (6 patients) were given as 2-h i.v. infusions on days 1, 3, 5, 8, 15, 22 and 29 for one cycle only. Neoadjuvant hormone therapy, consisting of buserelin acetate and flutamide, was administered concurrently. Prostatectomy specimens were then used to evaluate for clusterin expression for both interpatient and intrapatient comparisons with baseline. In this way, changes in expression of clusterin could be correlated to the dose of drug received and drug levels within the prostate tissue itself could be determined. In this study, treatment was well tolerated and custirsen produced statistically significant dose-dependent effects on suppression of clusterin expression in normal and tumor tissue. With this design and the use of these pharmacokinetic and pharmacodynamic end points, an effective biologic dose of 640 mg was established for OGX-011 based on its ability to suppress clusterin mRNA by > 90% [34] in prostate cancer tissue. Furthermore, in the historical control specimens treated with and without neoadjuvant hormone therapy, the mean apoptotic indices were 9.0% (95% confidence interval [CI], 5.1 – 13.0) and 7.0% (95% CI, 4.2 – 9.9), respectively. The apoptotic index from patients treated at the lower two dose levels of OGX-011 was 7.1% (95% CI, 2.4 – 11.8) but at the 640-mg dose level, the mean apoptotic index was 21.2% (95% CI, 18.1 – 24.2). This is especially encouraging given the dose–response effect and that prostate tissues have relatively lower tissue concentrations of custirsen after systemic administration compared with other tissues in preclinical studies (see below).

Clusterin is also detectable in serum. In subsequent Phase I and II studies with custirsen, a consistent decrease in serum clusterin has been observed at the 640-mg dosing [35]. Thus, clinical data clearly indicate that custirsen is biologically active in humans at 640 mg and lower dosing.

3.3 Metabolism and pharmacokinetics

ASO metabolism is through degradation by endogenous plasma and intracellular nucleases, which are inhibited by the phosphorothioate backbone and 2′MOE modifications [30]. In general, ASO are rapidly cleared from plasma as a result of wide distribution into tissues, except for the brain as they do not cross the blood–brain barrier. After systemic administration, the highest ASO tissue concentrations can be found in the kidney, liver, spleen and lymph nodes.

In mouse and primate studies, plasma was rapidly cleared of custirsen in both species. Plasma concentrations of custirsen generally peaked at the end of the infusion period and then decreased in an apparent bi-exponential fashion, which included two distinct half-lives. The half-life values associated with the distribution phase were 0.47 – 1.02 h in the monkey. The apparent terminal elimination half-life was much slower (37.5 and 137.9 h in mouse and monkey, respectively) than the distribution phase and is thought to reflect a composite of the slow rates of elimination of drug from the various tissues. There was no suggestion of plasma accumulation or changes in plasma kinetics after multiple dosing. The plasma concentration–time profiles were dose-dependent, showing increased plasma concentrations in monkeys with increasing dose over the entire dose range evaluated (1 – 10 mg/kg/wk). Plasma AUC values appeared to increase dose-dependently, but somewhat more than dose-proportionally, over the entire dose range evaluated in monkeys. Hence, mean monkey plasma clearance values appeared to exhibit an inverse dose dependency over the evaluated dose range. The maximum concentration in monkeys increased proportionally with increasing doses.

Following systemic administration, custirsen was broadly distributed and found in most mouse and monkey tissues; mean concentrations of custirsen increased with dose in all tissues examined (except for brain). Approximately 90% of the oligonucleotide in tissues was the intact, full-length custirsen oligonucleotide. The highest concentrations of custirsen were found in kidney, spleen and liver, with generally lower levels noted in the reproductive organs (prostate, testes, ovaries and uterus). Drug concentrations in male monkey prostate tissue were detected following the lowest dose administered (1 mg/kg) and increased in a dose-dependent manner, with average concentrations in prostate exceeding 8 μg/g tissue (approximately 1 μM) at a dose of 10 mg/kg, which well exceed *in vitro* concentrations associated with a biological effect.

In humans, plasma pharmacokinetic parameters for custirsen have been as predicted from the preclinical studies. In the first-in-man study with custirsen (discussed above), mean plasma distribution half-life was 0.476 – 3.83 h, with a trend to longer values with higher doses. Average peak concentrations and AUC were dose-dependent and displayed proportional and predictable increases in a linear fashion. Mean maximum plasma concentrations at 640 mg dosing was 61.1 μg/ml (95% CI, 55.3 – 66.9) after the day 1 infusion and 69.9 μg/ml (95% CI, 64.8 – 74.9) after the day 29 infusion. Clearance was similar across all subjects and occasions. Overall, there was no sign of plasma accumulation from the repetitive dosing [34]. Similar pharmacokinetic parameters were observed when custirsen was combined with docetaxel, in either a weekly or every-3-weekly schedule, or with gemcitabine/cisplatin chemotherapy [36].

Tissue concentrations associated with biologic effect have also been attained in humans [34]. The first-in-man Phase I study with custirsen using the neoadjuvant design (described above) also permitted an assessment of the prostate and lymph node specimens for tissue levels of custirsen. At doses of 320 mg and higher, concentrations of full-length custirsen that have been associated with a preclinical effect were achieved in the prostate, and a biologic effect – dose-dependent inhibition of clusterin expression in prostate cancer cells – was observed. There were dose-proportional increases in OGX-011 tissue concentrations and no apparent effect of timing of surgery (performed within 7 days of the last dosing) on OGX-011 tissue concentrations. Mean tissue concentrations at the 320-mg, 480-mg, and 640-mg dose levels were 1.67 (95% CI, 1.07 – 2.26), 2.29 (95% CI, 1.31 – 3.27), and 4.82 (95% CI, 3.54 – 6.10) μg/g of prostate tissue, respectively, corresponding roughly to concentrations of 223 nM, 306 nM, and 644 nM.

3.4 Clinical activity

To date, 294 patients have been treated with custirsen in six Phase I and II clinical trials. The first-in-man Phase I study was a neoadjuvant trial with custirsen given prior to radical prostatectomy in 25 men with localized prostate cancer [34]. A Phase I trial of docetaxel and custirsen accrued 40 patients with pathologic diagnoses of cancers that had been reported in the literature to express clusterin [35]. A single-arm Phase I/II trial accrued 85 patients with non-small cell lung cancer to a combination treatment of custirsen and gemcitabine-cisplatin chemotherapy [36]. Two Phase II trials of docetaxel and custirsen combination therapy have been conducted: a single-arm Phase II trial in patients with metastatic breast cancer, which enrolled 15 patients [37], and a randomized Phase II trial in patients with castration-resistant prostate cancer who were chemotherapy-naive accrued 81 patients in total [37]. Finally, a randomized Phase II trial has evaluated the combination of mitoxantrone or docetaxel in combination with custirsen in patients with castration-resistant prostate cancer that had progressed after prior docetaxel chemotherapy [38]. Randomized Phase III trials are currently in the planning stages.

In the Phase I docetaxel-custirsen combination study, 32 patients were evaluable for response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [39]. Two patients, both with hormone-refractory prostate cancer and chemotherapy-naive, had a confirmed partial response. Eleven patients had stable disease as best response (median duration, 6.5 months; range, 1.5 – 26.4 months). One of

these patients had ovarian cancer (previously treated with paclitaxel and carboplatin), and subsequently achieved a complete response in measurable disease while on follow-up, without further therapy; she remains in complete remission 4 years after completing protocol therapy. Fourteen patients with hormone-refractory prostate cancer were evaluable for post-treatment prostate-specific antigen (PSA) declines, with three patients having had prior chemotherapy with mitoxantrone or docetaxel. Six patients had a confirmed PSA response (defined as a post-treatment PSA decline of ≥ 50% from baseline, confirmed by a second value); one patient had an unconfirmed PSA response; and two patients had unconfirmed PSA decreases of 29 and 30% [36].

In the study for non-small cell lung cancer, 12 confirmed partial responses were observed (objective response rate = 23%) and median progression-free survival was 101 days (range: 53 – 260+). Of the first 24 patients who had been followed for 1 year, median survival was 383 days (19 – 751+), with 14 patients (58%) surviving > 1 year. This overall survival data were considered clinically significant compared with prior clinical trial data evaluating chemotherapy alone.

A single-arm Phase II trial of docetaxel and custirsen for patients with metastatic breast cancer initially evaluated 15 patients. Five partial responses were observed (objective response rate 33%), but this just fell short of the *a priori* hypothesis for continuation to the second stage of the study (response rate of ≥ 35%) [37]. It is debatable whether the RECIST criteria response rate in a relatively small single-arm trial is a sensitive indicator of the clinical activity of an agent such as custirsen, which aims to improve chemosensitivity.

Because of this difficulty of interpreting antitumor responses of combination chemotherapy with a targeted agent, especially in patients with castration-resistant prostate cancer, a randomized Phase II study was carried out in this population. Patients with chemo-naive, metastatic castration-resistant prostate cancer were randomized to receive either the docetaxel-custirsen combination, or docetaxel alone, as an internal control arm; initial results have been presented [38]. Forty patients received combined therapy and 41 received standard docetaxel chemotherapy. The median cycles delivered for combined docetaxel-custirsen was eight cycles, and only six for docetaxel standard therapy. The PSA response rate (≥ 50% decline from baseline, confirmed by a subsequent value) was similar for both arms, at approximately 50%. However, in the combination arm, there were no patients whose best PSA response was progression, whilst on the docetaxel standard therapy arm, 10% of patients had progression as best response. Progression-free survival is currently 7.3 months (95% CI, 5.2 – 9.3) and 5.9 months (95% CI, 3.6 – 10.7) for the combination docetaxel-custirsen and standard therapy arms, respectively. Patients continue to be followed for progression and overall survival.

A further trial in patients with castration-resistant prostate cancer has recently been completed and initial results presented [40]. In this study, patients were included only if they had previously progressed on docetaxel within 6 months of study entry, and randomized to receive either docetaxel or mitoxantrone both combined with custirsen, thus evaluating the hypotheses that custirsen could reverse docetaxel resistance or improve mitoxantrone efficacy in a chemotherapy-resistant population. Forty-two patients received at least one cycle of combined therapy, the median number of cycles delivered for the docetaxel-custirsen being 7.5 cycles, and mitoxantrone-custirsen, 6.0 cycles. PSA declines of ≥ 90, ≥ 50 and ≥ 30% were seen in 20, 40 and 55% of patients receiving docetaxel-custirsen and 0, 27 and 32% of patients receiving mitoxantrone-custirsen. Pain responses were also seen in 67 and 50% of patients receiving docetaxel-custirsen and mitoxantrone-custirsen, respectively. At a median follow-up of 13.3 months, 60% of patients were still alive in both arms. These results are of interest considering the docetaxel-resistant state of their disease, with a usually reported median survival for patients receiving second-line chemotherapy being around 10 – 12 months and PSA response rates in the order of ≤ 20% [41].

4. Safety and tolerability

In preclinical toxicity studies, there no clinical signs of toxicity observed at doses of up to 50 mg/kg in mice or of up to 10 mg/kg in monkeys. The primary toxicities were alterations in liver function in the form of elevated transaminase in mice at a dose of 50 mg/kg, immune stimulation in the form of lymphohistiocytic cell infiltrates in mice, and minor evidence of complement activation related to peak concentration in monkeys at 10 mg/kg.

In the first-in-man study [34], dose-limiting toxicity was not observed at any of the dose levels evaluated and adverse events were limited to grade 1 or 2 only. Toxicity appeared to be dose-related, tending to occur within the first week and diminish with continued dosing. Grade 1 leukopenia and thrombocytopenia were observed, with thrombocytopenia increasing in frequency with higher dose ($p = 0.04$), three of six patients experiencing grade 1 thrombocytopenia and two of six experiencing grade 1 leukopenia at the 640-mg dose level. Grade 1 anemia was seen in 19 of the 25 patients, but did not appear to be dose-dependent ($p = 0.44$). The most common non-hematologic adverse events were fever, fatigue and rigors, which usually occurred several hours after completion of the infusion and tended to be self-limiting. Fever and rigors appeared to be dose-related ($p = 0.001$ and $p < 0.0001$, respectively), with five of six patients at the 640-mg dose level experiencing fatigue and fevers, and all six patients experiencing rigors at that dose level. The fever and rigors typically occurred on the day 1 and 3 infusions, lessened after the day 5 infusion, and did not occur with the day 8 and subsequent infusions.

Grade 1 and 2 elevations in hepatic transaminases were also observed. At the 640-mg dose level, four of six subjects had increases in their AST and ALT, with two of the

six subjects experiencing grade 2 AST and/or ALT elevation. Elevated hepatic transaminases were observed to occur by day 8, but resolved to grade 1 or less by day 15 – 22 despite continuation of OGX-011 therapy. There was no apparent dose-dependent induction of serum complement C3a.

With custirsen in combination with chemotherapy, there does not appear to be a clinically significant worsening of chemotherapy-related side effects. Standard doses of docetaxel [35] or gemcitabine and cisplatin [36] could be safely delivered with biologically active doses of custirsen. In the randomized study of docetaxel-custirsen combination versus docetaxel alone [38], there was no increase in the occurrence of grade 3/4 or serious adverse events. Toxicities that were more common in the combination treatment included the typical acute side effects with custirsen seen in prior studies (fever, rigors, sweating) but also neuropathy, limb edema and lymphopenia.

5. Conclusion

Cytoprotective chaperone proteins regulated by HSF1, such as heat-shock proteins and the related clusterin protein, have emerged as interesting targets for cancer therapeutics. Custirsen (OGX-011) is a next-generation antisense molecule that incorporates 2′MOE modifications and a phosphorothioate backbone, permitting an extended tissue half-life, less non-sequence-specific toxicity, and an intermittent dosing regimen. Early-phase clinical trials in humans with custirsen have demonstrated not only its tolerability but also, importantly, its biological activity in inhibiting the expression of clusterin in cancer and normal tissues. The current clinical development of custirsen is in combination with chemotherapy, and several Phase II trials have been reported in a preliminary fashion with encouraging response rates and survival data. Randomized Phase III studies are in the planning stages.

6. Expert opinion

Custirsen has significant advantages over prior phosphorothioate antisense therapeutics as custirsen incorporates newer chemistry, allowing greater potency and tolerability, and an easier delivery schedule in preclinical studies. The early-phase clinical trials with custirsen have been elegantly performed, with evidence of dose-responsive biologic effects. The biologic activity with custirsen has been clearly demonstrated with inhibition of clusterin expression in tumor and normal tissues, thus validating the antisense approach to targeting the expression of putative genes in humans.

Phase II studies with custirsen have been preliminarily reported in patients with prostate, breast and lung cancer. These indicate that treatment with custirsen is well tolerated in combination with standard doses of chemotherapy. Interpretation of the response and survival data are more difficult, given the limited sensitivity of Phase II end points to identify agents that can enhance chemotherapy sensitivity and the design of the studies being single-armed and/or of limited power.

In patients with metastatic castration-resistant prostate cancer and docetaxel-resistant disease, encouraging responses were seen with re-treatment with docetaxel when combined with custirsen in an exploratory Phase II trial. A Phase III randomized study is now planned in this population, with patients randomized to receive either re-treatment with docetaxel or docetaxel plus custirsen, with overall survival as the primary end point. If positive, this would be the first antisense therapeutic to demonstrate clinical benefit in patients with cancer. Subsequent trials could be aimed at combining custirsen with standard systemic therapy in other major cancers that express clusterin, including colorectal, lung, ovary, bladder, and kidney cancers.

Demonstration of clinical benefit with custirsen would also validate the antisense approach as a systemic therapy application for malignancy, opening the door to a host of therapeutic targets that are not amenable to small-molecule or antibody inhibition.

Declaration of interest

Dr Gleave would like to disclose his involvement with Oncogenex, Sanofi-Aventis and AstraZeneca.

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